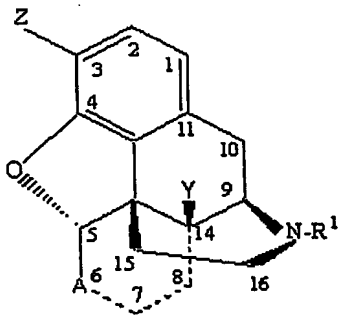
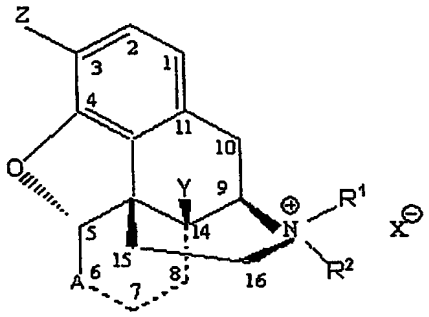
CLAIMS

1. A process for the preparation of a quaternary derivative of a tertiary N-substituted morphinan alkaloid, the process comprising contacting a tertiary N-substituted morphinan alkaloid substrate with an alkylating agent in an anhydrous solvent system wherein the solvent system comprises an aprotic dipolar solvent with the aprotic dipolar solvent constituting at least 25 wt% of the solvent system, the tertiary N-substituted morphinan alkaloid substrate has the structure of Formula 1 and the quaternary derivative has the structure of Formula 1A:



Formula 1



Formula 1A

wherein

A is -C(O)-, -C(S)-, -C(=CH_2)-, -CHA_1- or -CA_1=,

A_1 is hydroxy, alkoxy, or acyloxy,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl,

X^e is an anion,

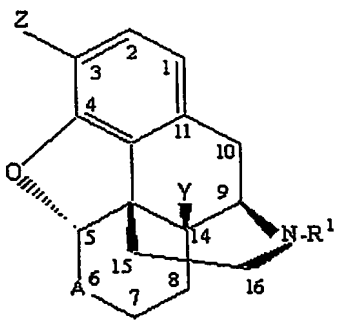
Y, if present, is hydrogen, hydroxy, alkoxy, or acyloxy,

Z is hydroxy, alkoxy, or acyloxy, and

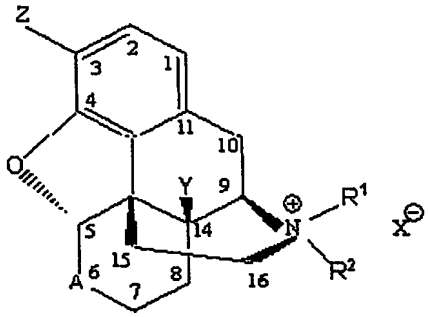
the dashed lines between the carbon atoms at positions 6 and 7, 7 and 8, and 8 and 14, respectively, represent (i) carbon-carbon single bonds, (ii) carbon-carbon single bonds between positions 6 and 7 and between positions 8 and 14, and a double bond between positions 7 and 8, or (iii) conjugated carbon-carbon double bonds between positions 6 and 7 and positions 8 and 14, with the

proviso that Y is not present if there is a double bond between the carbons at positions 8 and 14.

2. The process of claim 1 wherein the tertiary morphinan alkaloid substrate is represented by Formula 2 and the quaternary derivative is represented by Formula 2A.



Formula 2



Formula 2A

wherein

A is -C(O)-, -C(S)-, -C(=CH_2)-, or -CHA_1-,

A_1 is hydroxy, alkoxy, or acyloxy,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl, and

$X^\ominus$ is an anion,

Y, is hydrogen, hydroxy, alkoxy, or acyloxy, and

Z is hydroxy, alkoxy, or acyloxy.

3. The process of claim 2 wherein the tertiary morphinan alkaloid substrate is naltrexone ((5α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one), oxymorphone ((5α)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one), oxycodone ((5α)-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one), hydromorphone ((5α)-4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one), naloxone ((5α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one), nalmefene ((5α)-17-(cyclopropylmethyl)-4,5-epoxy-

6-methylenemorphinan-3,14-diol) or nalbuphine ((5α)-17-(cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol).

4. The process of claim 3 wherein the alkylating agent is methyl bromide.

5. The process of claim 2 wherein the alkylating agent is methyl bromide.

6. The process of claim 1 wherein the alkylating agent is methyl bromide.

7. The process according to claim 1 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

8. The process according to claim 4 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

9. The process according to claim 5 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

10. The process according to claim 6 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

11. The process according to claim 1 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

12. The process according to claim 7 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

13. The process according to claim 8 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

14. The process according to claim 9 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

15. The process according to claim 1 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

16. The process according to claim 2 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

17. The process according to claim 4 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

18. The process according to claim 5 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

19. The process according to claim 6 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

20. The process according to claim 7 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

21. The process according to claim 8 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

22. The process according to claim 9 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

23. The process according to claim 10 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

24. The process according to claim 11 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

25. The process according to claim 12 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

26. The process according to claim 13 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

27. The process according to claim 14 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

28. The process according to claim 1 wherein Y and Z are independently -OCH_3, -OAc, -OTHP, -$OSiR_3$, -*OBn*, -OBz, -OBs, -OTs, or -OMs wherein each R is independently hydrocarbyl.

29. The process according to claim 1 wherein said anhydrous solvent system contains less than 0.2 wt.% water and is maintained in a moisture-free atmosphere in a reaction vessel.

30. The process according to claim 1 wherein said anhydrous solvent system contains less than 0.1 wt.% water.

31. The process according to claim 1 wherein said anhydrous solvent system contains less than 0.05 wt.% water.

32. The process according to claim 31 wherein said alkylating agent is a methylating agent.

33. The process according to claim 31 wherein said alkylating agent is methyl bromide.

34. The process according to claim 31 wherein said alkylating agent and said substrate are present in a mole ratio of between 1:1 and 1.5:1, respectively.

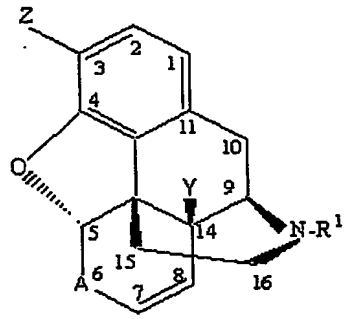
35. The process according to claim 31 wherein said alkylating agent and said substrate are present in a mole ratio of about 1.25:1, respectively.

36. The process according to claim 1 wherein said anhydrous dipolar

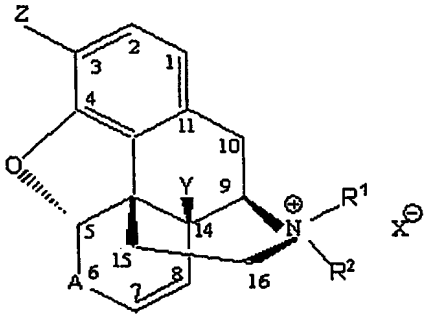
aprotic solvent and said substrate are present in a volume-to-weight ratio of 1.5:1 -1.75:1.

37. The process according to claim 1 wherein said reaction is carried out within a temperature range of 55-85°C.

38. The process of claim 1 wherein the tertiary morphinan alkaloid substrate is represented by Formula 3 and the product is represented by Formula 3A.



Formula 3



Formula 3A

wherein

A is -C(O)-, -C(S)-, -C(=CH_2)-, or -CHA_1-,

A_1 is hydroxy, alkoxy, or acyloxy,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl, and

X^e is an anion,

Y, is H, hydroxy, alkoxy, or acyloxy, and

Z is hydroxy, alkoxy, or acyloxy.

39. The process of claim 38 wherein the tertiary morphinan alkaloid substrate is morphine ((5α,6α)-7,8-didehydro-4,5-epoxi-17-methylmorphinan-3,6-diol), codeine ((5α,6α)-7,8-didehydro-4,5-epoxi-3-methoxy-17-methylmorphinan-6-ol), codeinone ((5α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one) or 14-hydroxy-codeinone ((5α)-7,8-didehydro-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one).

40. The process of claim 38 wherein the alkylating agent is methyl bromide.

41. The process of claim 39 wherein the alkylating agent is methyl bromide.

42. The process according to claim 38 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

43. The process according to claim 39 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

44. The process according to claim 40 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

45. The process according to claim 41 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

46. The process according to claim 38 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

47. The process according to claim 39 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

48. The process according to claim 40 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

49. The process according to claim 42 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

50. The process according to claim 1 wherein the morphinan alkaloid substrate is thebaine.

51. The process of claim 50 wherein the alkylating agent is methyl bromide.

52. The process according to claim 50 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

53. The process according to claim 51 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

54. The process according to claim 50 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

55. The process according to claim 51 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

56. The process according to claim 55 wherein the aprotic dipolar solvent constitutes at least 75 wt.% of the solvent system.

57. A process for separation of a liquid mixture of a 3-alkoxymorphinan alkaloid from a 3-hydroxymorphinan alkaloid, the process comprising,

contacting the mixture with a strong base, thereby converting the 3-hydroxy morphinan alkaloid to a salt,

precipitating the salt but not the 3-alkoxymorphinan alkaloid from the liquid, and

separating the salt precipitate from the 3-alkoxymorphinan.

58. The process in claim 57 wherein said strong base is selected from sodium methoxide, sodium hydroxide, and potassium hydroxide.

59. The process in claim 57 wherein said methanol/water mixture is present in a volume ratio of about 2:1.

60. The process in claim 57 wherein said pH is adjusted with hydrobromic acid.

61. The process of claim 57 wherein the 3-alkoxymorphinan is a quaternary, 3-methoxy derivative of naltrexone or naloxone.